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Drug-Eluting Introducer Sheath Prevents Local Peripheral Complications

Pre-Clinical Evaluation of Nitric Oxide–Coated Sheath

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Objectives This study evaluated the protective effect of nitric oxide–coating of introducer sheath on the local complications in juvenile porcine femoral arteries with similar size to human radial arteries.

Background Insertion of an introducer sheath induces vasospasm and transient or permanent vessel occlusion of radial arteries.

Methods Nitric oxide–coated or control introducer sheaths with or without spasmolytic cocktail (control + C-sheath) were inserted into porcine femoral arteries, followed by percutaneous coronary intervention (PCI). The diameter of the femoral artery at the puncture site, distally and proximally, was measured by quantitative angiography. Histopathological and histomorphometric parameters of the femoral arteries were analyzed 1 h or 1 week after PCI.

Results Insertion of femoral sheath led to mild or severe spasms, with significantly higher vessel diameter at the access site (2.69 ± 0.81 mm vs. 1.77 ± 0.77 mm and 1.85 ± 0.66 mm, $p < 0.001$), and proximal and distal to it, during PCI in the nitric oxide–sheath group versus the control-sheath and control + C-sheath groups, respectively. Immediately following PCI, significantly less luminal thrombosis (12% vs. 33% and 31% of all analyzed segments, $p < 0.001$) was observed in the nitric oxide–sheath arteries. At 1 week, lower intimal inflammation score (0.43 ± 11 vs. 1.03 ± 0.35 and 1.04 ± 0.32, $p < 0.05$), less luminal thrombosis (8% vs. 21% and 30% $p < 0.05$), and smaller intimal hyperplasia (0.31 ± 0.31 mm^2 vs. 0.47 ± 1.00 mm^2 and 0.86 ± 0.82 mm^2, $p < 0.05$) were observed in NO-sheath arteries at the injury site.

Conclusions Nitric oxide coating on the introducer sheath prevents local complications during PCI and results in less vascular thrombosis and inflammation at the access site, contributing to patency of the access vessel with similar size to the radial artery. (J Am Coll Cardiol Intv 2011;4:98–106)

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Insertion of an introducer sheath in the peripheral artery for percutaneous coronary angiography or percutaneous coronary intervention (PCI) may cause local complications at the access site, such as local arterial spasms, dissection, arterial stenosis, or occlusion, especially using the transradial approach (1–3). Most invasive cardiology centers traditionally use the femoral access for coronary angiography and PCI, but the transradial approach is becoming more popular due to economic considerations (early mobilization of the patients), and less local bleeding complications (4,5). Definitive hand ischemia is negligible at the radial access site due to the deep and superficial palmar arches. Moreover, the radial artery can be compressed easily and effectively to achieve a primary hemostasis, even if the patient receives aggressive antithrombotic treatment (6).

On the contrary, severe local complications, such as periprocedural spasms of the radial artery, occur in up to 9% and occlusions in up to 6% of cases (7). A recent optical coherence tomography study of the radial artery revealed intimal tear in 32%, medial dissection in 16%, and thrombosis in 20.5% of cases after sheathing (8). To circumvent these limitations, several strategies have been developed, such as hydrophilic coating of the sheaths for reduction of friction (9), short sheaths with smaller lumen diameter (2,3,10), and local or systemic administration of various vasodilators, such as calcium-channel blocker, nitrovasodilators, alone or in combination, as a spasmolytic cocktail (2,11). Nevertheless, the dramatic increase in the number of diagnostic coronary angiography and PCI with frequent intentions to repeat both procedures in the same patient, and the use of radial artery for bypass conduit necessitates new approaches to prevent severe local complication and occlusion of the radial artery after coronary procedures.

Nitric oxide (NO) is a potent vasodilator with an inhibitory effect on platelet aggregation and proliferation of vascular smooth muscle cells, reducing thrombus and neointimal formation (12). Theoretically, coating of radial introducer sheaths with NO might beneficially influence vasospasm, and the consequent local vascular complications.

Accordingly, the aim of our study was to investigate the effect of an NO-coated introducer sheath on mechanically induced, PCI-related local peripheral vasospasm and occlusion of the artery, as well as on the histological changes of the femoral arteries of juvenile pigs, with similar vessel size to human radial or cubital arteries.

Methods

NO-eluting sheath. The NO-eluting sheath (Millimed A/S, Roskilde, Denmark) was produced by Thomas Medical Products, Inc. (Malvern, Pennsylvania) and then coated, packed, and electron-beam sterilized. The NO-eluting coating was constructed as a "base coat" containing a combination of a NO-loaded linear polyethyleneimine, polyurethanes, and a polymeric matrix, and a "top coat" with only a polymeric matrix. The NO-loaded linear polyethyleneimine releases NO when it is exposed to a proton-donating (H^+) environment such as blood. Incorporating the NO-loaded linear polyethyleneimine into a polymer matrix along with top coating allows the controlled release of NO over 2 h. The NO-coated sheath had a release rate of 0.5 to 7.0 nmol/l NO/min/cm^2, which is considered within the therapeutic window, without toxic effects. Nitric oxide is delivered into the surrounding tissues of the vessel wall by dispersed diffusion from the sheath. The diffusion of NO from catheters coated using the same technology was tested in isolated rat aorta and human vessels, demonstrating the inhibition of norepinephrine-induced vasoconstriction (13).

Animal preparation. Twenty-eight domestic pigs (weight 12 to 15 kg) were fasted overnight and then sedated with 12 mg/kg ketamine hydrochloride and 1 mg/kg xylazine and 0.04 mg/kg atropine. After pre-medication, the anesthesia was deepened with isoflurane and O_2 via a mask. After intratracheal intubation, the anesthesia was maintained with 1.5 to 2.5 vol% isoflurane, 1.6 to 1.8 vol% O_2, and 0.5 vol% N_2O.

One day before the procedure, a loading dose of 250 mg aspirin and 300 mg clopidogrel were administered orally. Access to the right or left femoral artery was performed through direct puncture of the artery under sterile conditions, and a 6-F introducer sheath, either a NO-coated device or a noncoated control device (Radiofocus Introducer II, 6-F, Terumo Medical Corporation, Somerset, New Jersey) was inserted into the artery, in a randomized fashion in the arteries of 20 pigs (Fig. 1). After insertion of a control sheath, 10 ml vasodilation cocktail containing of 0.1 mg nitroglycerin, 1 ml lidocaine (2%), and 2.5 mg verapamil was administered intra-arterially via the sheath in the next 8 pigs (control + C-arteries).

Abbreviations and Acronyms

NO = nitric oxide

PCI = percutaneous coronary intervention

After administration of 100 IU/kg of heparin sodium, angiographies of the femoral and iliac arteries were performed with regular contrast media (Ultravist, Bayer, Leverkusen, Germany) and a 6-F–guiding catheter (Hockey stick, Cordis Cardiology, Miami Lakes, Florida) was advanced into the ascending aorta. The coronary angiography was followed by PCI simulating the shear stress of the femoral arteries during the mechanical manipulation of the catheter with wires and balloons. After PCI, the guiding catheter was removed and the angiography of the femoral artery was repeated, and the sheaths were removed. Ten animals with either NO-sheath or control sheath, and 4 pigs from the control + C-sheath group were euthanized, and a percutaneous closure of the puncture site was performed with an Angio-Seal (St. Jude Medical, St. Paul, Minnesota) closure device in the remaining 14 pigs (Fig. 1), replacing

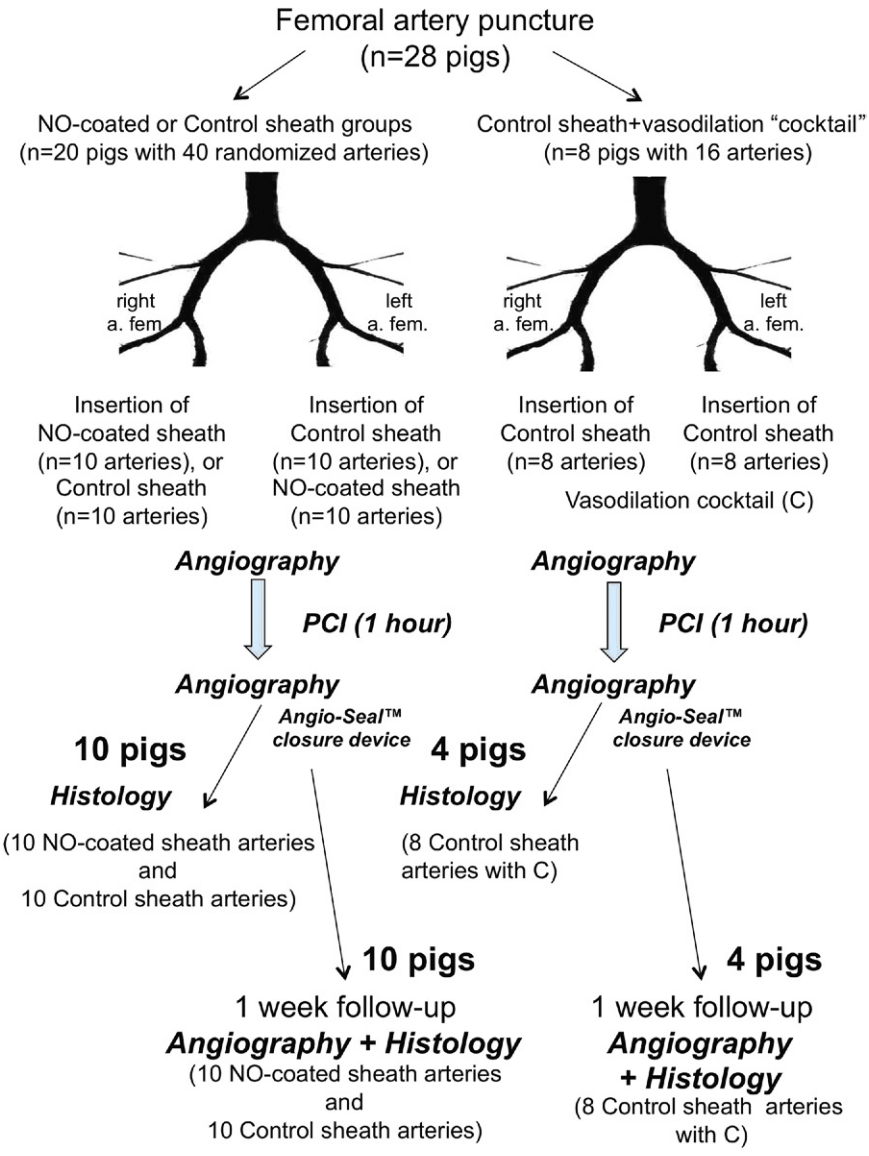

Figure 1. Study Design

Flow diagram depicting the study design. Twenty femoral arteries (right and left) of 20 pigs were randomized to receive either control sheath or nitric oxide (NO)-coated sheath, whereas the contralateral artery received the other type of the sheath. Additionally, 8 pigs received control sheaths in both (right and left) femoral arteries and vasodilation cocktail was locally injected. a. fem. = arteria femoralis; PCI = percutaneous coronary intervention.

the original sheath by the Angio-Seal sheath. After removal of the guidewire, hemostasis was achieved by the mechanical means of the anchor-arteriotomy-collagen sandwich of the device, which is supplemented by the coagulation-inducing properties of the collagen (14). These pigs were allowed to recover and survived for 1 week after PCI, and then they were euthanized. The euthanasia was performed with 10 ml saturated potassium chloride, and the femoral arteries were harvested for histomorphometric and histopathological assessments.

Follow-up examinations. During the 1-week follow-up period, daily doses of 100 mg aspirin and 75 mg clopidogrel were administered orally. After 7 days, control angiography of the femoral arteries was performed through a carotid artery access to figure both (left and right) femoral arteries, under general anesthesia. Subsequently, the animals were euthanized. The experiments were conducted at the Institute of Diagnostics and Radiation Oncology (University of Kaposvar, Kaposvar, Hungary). The animal investigations conform to the "Position of the American Heart Associa-

tion on Research Animal Use," adopted by the American Heart Association on November 11, 1984. All animal facilities met the standards of the American Association for Accreditation of Laboratory Animal Care.

Quantitative assessment of femoral angiography. Periprocedural and follow-up angiographic parameters of the peripheral arteries were evaluated using a computer-assisted quantitative angiographic edge detection algorithm (quantitative coronary angiography, ACOMPC, Siemens, Germany), by an independent observer blinded to the experimental conditions. The vessel diameter at the access site and the diameters proximal and distal to the puncture site were measured, immediately after sheath placement, at the end of the PCI (at 1 h), and after 1 week in the surviving animals.

Histopathology and histomorphometry of the femoral arteries. The harvested femoral arteries were flushed with approximately 100 ml saline and then pressure fixed in situ with 4% buffered formaldehyde for 20 min. Afterward, the arteries were fixed in formalin and embedded in paraffin. The segments of the Angio-Seal sites (proximal and distal 1 cm) were not included in the analyses. The following segments of the femoral arteries have been sectioned: serial sections of the artery proximal to the access site cut into 10 segments (1 cm of each), and proximal and distal reference segments within 2 cm proximal to sheath end and 2 cm distal to the puncture site. Sections of each arterial segment were stained with hematoxylin-eosin. All segments of the arteries were evaluated separately by an experienced observer blinded to the groups, and the mean values of the quantitative histopathological and histomorphometric parameters of 1 artery were entered into the statistical analysis.

The quantitative histopathological (15) analysis included the scores of intimal and adventitial inflammation, fibrin deposition, and presence of thrombus. Intimal inflammation was scored from 0 to 3 as absent, mild, moderate, or heavy inflammation, involving <10%, 10% to 25%, or >25% of the circumference of the intima, respectively. Adventitial inflammation score was graded as 0 for no inflammation; 1 for mild inflammatory infiltration or focally moderated in <25% of the vessel area in media or adventitia; 2 for moderate inflammatory infiltration or focally marked in 25% to 50% of the vessel area in media or adventitia; 3 for heavy inflammatory infiltration or focally marked in >50% of the vessel area in media or adventitia. Fibrin score was graded from 0 to 3 as no fibrin deposition or mild, moderate, or heavy fibrin deposition, involving <10%, 10% to 25%, or >25% of the circumference of the vessel, respectively. Necrosis and hemorrhage were scored from 0 to 3 as no change, mild, moderate, or heavy changes in any layer of the vessel, involving 0%, 1% to 10%, 10% to 25%, or >25% of the circumference of the vessel, respectively. Furthermore, the presence of mural thrombus was identified.

The histomorphometric analysis included the lumen, internal elastic lamina, media, external elastic lamina, adventitial areas, and percent area stenosis. The area between the lumen and internal elastic lamina was defined as the area of platelet and leukocyte attachment to the intima and mural thrombus at 1-h follow-up and as neointimal area at 1-week follow-up.

Statistics. Continuous parameters of the arteries of different groups (all of them showing normal distribution) were expressed as mean ± SD. Categorical variables were characterized as percentages. The continuous variables of the sheath-groups were compared by analysis of variance supplemented by Student *t* test. Differences in categorical variables were evaluated by chi-square test and Fischer exact test. Statistical analyses were carried out using SPSS software (version 17.0, SPSS, IBM Corporation, Somers, New York). A p value of <0.05 was considered statistically significant.

Table 1. Quantitative Angiographic Results of the Femoral Arteries After NO-Eluting (NO-Sheath) and Control Sheath Placement (Control Sheath and Control + C-Sheath With Vasodilation Cocktail)

Time	Sheath Group	Vessel Diameter at the Puncture Site (mm)	Vessel Diameter Proximal to Puncture Site (mm)	Vessel Diameter Distal to Puncture Site (mm)
After sheath placement	NO-sheath (n = 20 arteries)	2.30 ± 1.13	4.28 ± 0.55	3.03 ± 0.42
	Control sheath (n = 20 arteries)	2.03 ± 0.64	4.04 ± 0.52	2.62 ± 0.62
	Control + C-sheath (n = 16 arteries)	2.09 ± 0.71	4.11 ± 0.51	2.65 ± 0.59
	p values	NS	NS	NS
After coronary intervention	NO-sheath (n = 20 arteries)	2.69 ± 0.81	4.27 ± 0.40	3.37 ± 0.46
	Control sheath (n = 20 arteries)	1.77 ± 0.77*	3.77 ± 0.42*	2.74 ± 0.53*
	Control + C-sheath (n = 16 arteries)	1.85 ± 0.66*	3.75 ± 0.45*	2.62 ± 0.44*
	p values	<0.001	<0.001	<0.001
At 1-week follow-up	NO-sheath (n = 10 arteries)	4.24 ± 0.92	4.74 ± 0.80	4.02 ± 0.69
	Control sheath (n = 10 arteries)	4.02 ± 0.99	4.12 ± 0.66	3.80 ± 1.10
	Control + C-sheath (n = 8 arteries)	4.10 ± 0.85	4.15 ± 0.54	3.81 ± 0.71
	p values	NS	NS	NS

The vessel diameter distal to the sheath placement is larger than that of the puncture site, due to spasm of the artery. The p values represent the results of analysis of variance. *p < 0.005 between nitric oxide (NO)-sheath versus control sheath and control + C-sheath by *t* test. *p < 0.005 between nitric oxide (NO)-sheath versus control sheath and control + C-sheath by *t* test.

Results

Quantitative coronary angiography. The animals with control + C-sheath exhibited an insignificant systolic pressure drop immediately after intra-arterial administration of the antispasmodic cocktail (from 112 ± 13 mm Hg to 101 ± 14 mm Hg), which was not observed in the other animals.

Visually, most of the arteries were in spasm immediately after sheath placement as confirmed by quantitative coronary angiography, and the access site lumen diameter was even smaller than the diameter of the distal part of the arteries with all types of sheaths (Table 1, Fig. 2). A slightly larger vessel size at the proximal site was measured in the control + C-arteries, with no statistical difference between the groups. At the end of PCI, significantly larger vessel diameter of the femoral arteries with the NO-sheath was measured at the access site, as well as at the proximal and distal sites. At 1-week follow-up, no differences between the groups were noted (Table 1).

Histopathology of the femoral arteries. Histopathological analysis revealed the adhesion of leukocytes and platelets to the vessel wall endothelium at the access sites with signs of acute intimal and adventitial inflammation and hemorrhage 1 h after

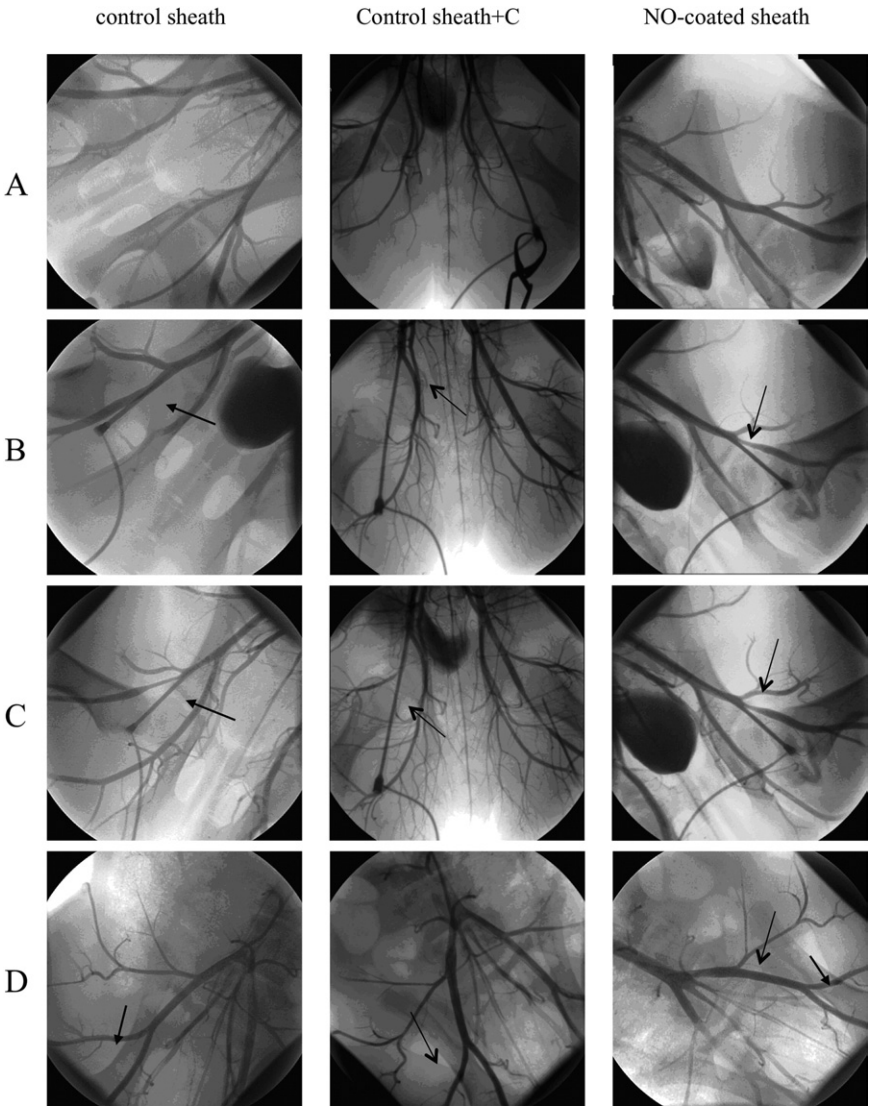

Figure 2. Representative Angiograms of the Femoral Arteries After Sheath Placement

Arteria femoralis angiograms before **(A)**, immediately after **(B)**, and 1 h **(C)** after placement of control or control with vasodilation cocktail and nitric oxide–coated sheaths, and 1 week after the coronary procedure **(D)**. Note that the arteries with the control sheaths are more spastic than the arteries with nitric oxide–eluting sheath, after sheath placement and at 1-h follow-up **(arrows)**. Complete occlusion of the femoralis artery after sheath placement (control sheath + C) **(middle B)**, with only partial recovery post-PCI **(middle C)**, and no abnormality at follow-up **(middle D)**. Abbreviations as in Figure 1.

PCI, without significant difference between the groups. However, small thrombus formation was observed significantly more often in the control sheath groups (Table 2).

After 1 week, significantly less intimal inflammation and presence of mural thrombi were found in the NO-sheath arteries compared with the control arteries (Fig. 3, Table 2).

Histomorphometry of the femoral arteries. The arteries of the NO-sheath group showed significantly smaller intimal area (consisting of mural thrombi, adhesive platelets, and leukocytes) and percent area stenosis at 1 h (Table 3), and smaller neointimal hyperplasia at the injury site at the 1-week follow-up (Table 4).

Discussion

To our knowledge, this is the first study presenting the spasmolytic, anti-inflammatory, and antithrombotic effect of the NO-eluting introducer sheath on the peripheral arteries. Nitric oxide released from the sheath diminished the vasoconstrictive response of the access artery, ensuring higher intraluminal diameter during the coronary procedure, which in turn makes the local peripheral manipulation safer. In addition, the local NO release inhibited thrombus formation and inflammatory reaction at the access site, contributing to the patency of the peripheral access artery following PCI at the vessel size of the human radial artery.

Benefits and disadvantages of distinct access sites. The major limitations of the radial access are the entry site failure with the necessity of crossover to an alternative access route, the higher radiation dose, the longer procedural time, and the occlusion or spasm of the radial artery. These drawbacks may offset the benefits of this access mode, hindering the switch from femoral to radial approach in most catheterization laboratories (16). Even if definitive complications, such as asymptomatic or symptomatic vessel closure, or development of significant neointima are rare, as radial access accounts for <10% of the procedures worldwide, and <1% in the U.S. (16), the absolute number is rapidly growing. Therefore, the prevention of the definitive vessel injury is important, especially in patients with expected repeat angiography or PCI or candidate for coronary bypass surgery with planned radial artery as conduit.

Shear stress of the access artery during coronary angiography and intervention. In daily practice, radial arterial spasm is manifested by the resistance against advancing the intra-arterial equipment and by the patient's complaint of forearm pain (17). Principally, the spasm is necessary for natural hemostasis; however, it might be harmful when a sheath lies in the artery. The radial artery has multiple tight muscle layers in the media, with higher density of smooth muscle cells compared with the femoral artery. The predominance of alpha-adrenoceptors in the radial artery leads to rapid vasoconstriction to shear stress-induced local release of catecholamines, serotonin, endothelin I, and angiotensin II (18). The subsequent spasm induces friction of the arterial wall in contact with the sheath, further increasing shear stress and leading to intimal tear or medial dissection not only at the access site, but also at the proximal and distal portion of the artery with subsequent thrombosis (8). Accordingly, the observed changes of porcine femoral arteries might even underestimate the histopathological alterations of a radial artery during catheterization. This is supported with the recently published optical coherence tomography study of human radial arteries (8).

Usually, the radial artery spasms can be sufficiently managed with intra-arterial spasmolytic cocktails (17). Immediate angiography post-sheathing revealed that most of the arteries are affected promptly after sheath placement, as the access site lumen diameter was even smaller than the diameter of the distal part of the artery, even after intra-arterial administration of the vasodilation cocktail.

NO-coated introducer sheath in the prevention of vascular inflammation and thrombosis. Acute vascular damage is known to induce a very early immune response with inflammatory cell invasion, increased extracellular matrix turnover, and oxidative stress (19). The introducer sheath causes a

Table 2. Histopathological Results of the Femoral Arteries After NO-Eluting (NO-Sheath) and Control Sheath Placement (Control Sheath and Control + C-Sheath With Vasodilation Cocktail), After Coronary Intervention and at 1-Week Follow-Up

Time	Sheath Group	Inflammation in the Intima (Score)	Inflammation in the Adventitia (Score)	Necrosis (Score)	Hemorrhage (Score)	Thrombosis (%)
After coronary intervention	NO-sheath (n = 10 arteries)	0.65 ± 0.32	0.05 ± 0.12	0	0.31 ± 0.38	12%
	Control sheath (n = 10 arteries)	0.87 ± 0.47	0.06 ± 0.15	0	0.21 ± 0.37	33%*
	Control + C-sheath (n = 8 arteries)	0.85 ± 0.44	0.06 ± 0.09	0	0.30 ± 0.28	31%*
	p value	NS	NS	NS	NS	<0.001
At 1-week follow-up	NO-sheath (n = 10 arteries)	0.43 ± 0.11	0.15 ± 0.15	0	0.14 ± 0.17	8%
	Control sheath (n = 10 arteries)	1.03 ± 0.35*	0.27 ± 0.34	0	0.33 ± 0.65	21%*
	Control + C-sheath (n = 8 arteries)	1.04 ± 0.32*	0.32 ± 0.11*	0	0.27 ± 0.22	26%*
	p value	<0.05	NS	NS	NS	<0.005

The p values represent the results of analysis of variance or chi-quadrate test, respectively. *p<0.05 between NO-sheath versus control sheath and control + C-sheath by *t* test, or Fischer exact test, respectively. Abbreviations as in Table 1.

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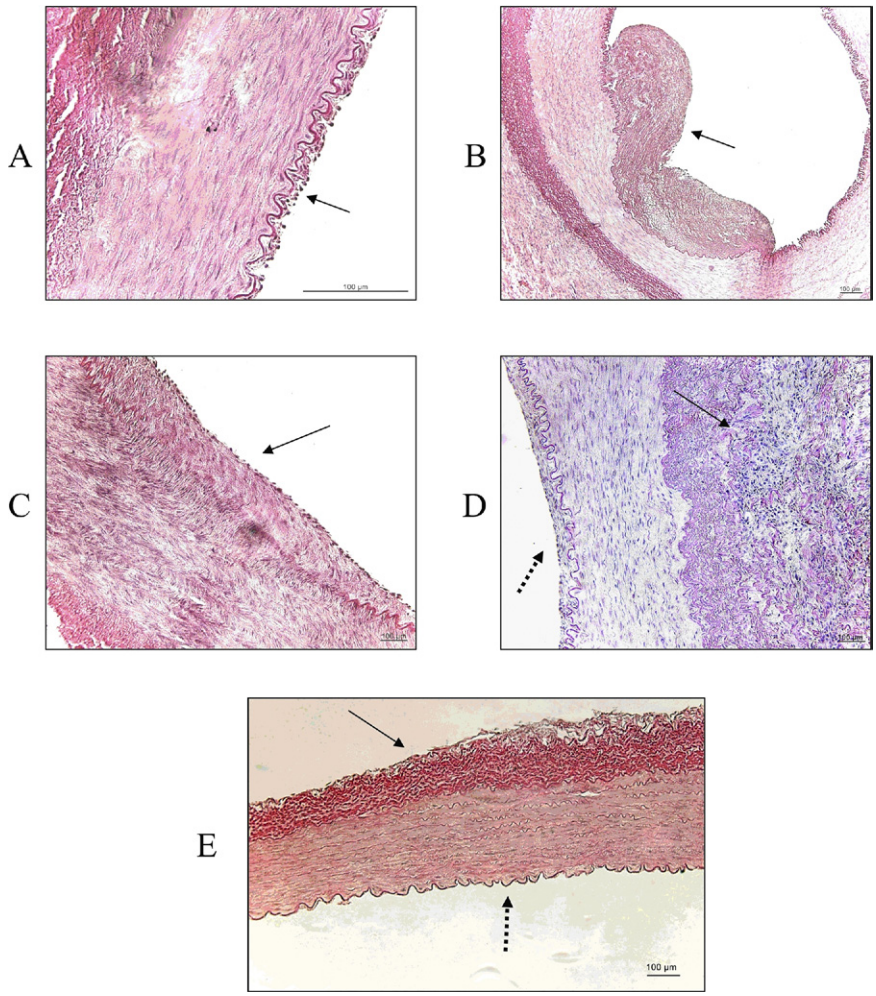

Figure 3. Representative Histological Images of the Femoral Arteries After Placement of Nitric Oxide–Coated Sheath and Control Sheath With or Without Additional Vasodilation Cocktail

Control sheaths **(A to D)**: platelet and leukocyte adhesion on the intima **(arrow)** 1 h after control sheath placement **(A)**, an organized thrombosis **(arrow) (B)**, moderate intimal hyperplasia **(arrow) (C)**, light intimal hyperplasia **(dotted arrow)** and inflammation **(arrow)** in the adventitia at 1-week follow-up **(D)**. Nitric oxide–coated sheath **(E)**: no intimal hyperplasia, no platelet or leukocyte adhesion on the intima **(dotted arrow)**, and no inflammation in the adventitia **(arrow)**.

mechanical vascular trauma, triggering pathological changes in the vessel (8).

In contrast, elution of NO from the coated sheath during PCI reduced the vasoconstriction and decreased the inflammatory and thrombotic reactions. More than 20% of the vessels showed mural thrombus, even a week after the coronary procedure, with increased intimal inflammation and neointimal hyperplasia. Although NO has a short half-life, the permanent contact with the vessel wall at the access site with continuous and stable elution from the NO-coated sheath seems to be sufficient to relieve vessel constriction and to inhibit platelet and leukocyte deposition, which might contribute to vascular healing and patency of the affected artery. Even, if the observed histological differences between the sheaths seem not to be relevant clinically at the first look, the histopathological changes and their frequency found in our animals are similar to that of the human radial arteries (8), shedding light to the high frequency of mostly unrevealed local complications.

Although our results may also be applied to the femoral arteries, the size of the access site of the juvenile porcine artery is similar to that of the human radial arteries (2.5 to 3.1 mm). Moreover, the femoral artery is less prone to spasm, and because of larger size in humans, the compromise of the vessel lumen resulting from intimal hyperplasia or small mural thrombus does not lead to ischemic limb complication.

Study limitations. In contrast with the potentially compromised human radial arteries with limited vasomotion, the femoral arteries of the juvenile pigs are healthy. However,

Table 3. Histomorphometric Results of the Femoral Arteries Immediately After PCI After NO-Eluting (NO-Sheath) and Control Sheath Placement (Control Sheath and Control + C-Sheath With Vasodilation Cocktail), After PCI

Sheath Groups (Post-PCI)	Lumen Area (mm^2)	Intimal Area (mm^2)	IEL Area (mm^2)	Media Area (mm^2)	EEL Area (mm^2)	Adventitia Area (mm^2)	%AS (%)
NO-sheath (n = 10 arteries)	3.18 ± 1.45	0.24 ± 0.27	3.42 ± 1.62	1.99 ± 0.71	5.41 ± 1.76	7.31 ± 2.41	6.8 ± 5.2
Control sheath (n = 10 arteries)	3.18 ± 1.66	0.33* ± 0.35	3.51 ± 1.86	1.90 ± 0.69	5.41 ± 1.92	7.01 ± 2.51	8.9* ± 6.3
Control + C-sheath (n = 8 arteries)	3.21 ± 1.46	0.36* ± 0.29	3.49 ± 1.33	2.02 ± 0.71	5.50 ± 2.04	7.29 ± 2.58	9.6* ± 6.9
p value	NS	<0.05	NS	NS	NS	NS	<0.05

Intimal area consisted of adhesive leukocytes and platelets and initial mural thrombosis. The p values represent the results of analysis of variance. *p < 0.005 between NO-sheath versus control sheath and control + C-sheath by *t* test.
%AS = percent area stenosis; EEL = external elastic lamina; IEL = internal elastic lamina; other abbreviations as in Table 1.

intravascular ultrasound obtained from radial arteries of patients undergoing transradial catheterization revealed significant plaque only in 8.6%, calcium deposition in 8.6%, and diffuse atherosclerosis in 6.9% of cases (20). The radial artery of pigs is too short, and because of the curvature of the brachialis and subclavian artery, a catheterization method similar to humans is impossible. Despite the differences between the human radial arteries and porcine (and human) femoral arteries, to our knowledge, there is no other relevant animal model for radial artery approach.

We have used saturated potassium chloride for euthanasia, which might cause acute vasoconstriction, influencing the histomorphometric results. However, saturated potassium chloride causes cardiac arrest within a few seconds and is a recommended agent for primary euthanasia (American Association for Accreditation of Laboratory Animal Care) in pigs.

The aspirin and clopidogrel doses were not adjusted for porcine weight. However, the doses of both medicines are standard for patient care with PCI, without weight adjustment, and for pre-clinical experiment involving coronary stenting in pigs.

In the surviving animals, we have closed the femoral puncture site with the Angio-Seal, which cannot be used in a human radial artery. However, the femoral arteries of pigs cannot be compressed safely without the fear of bleeding complication after recovery of the animals from anesthesia. To prevent the ligation of the femoral artery (which is the standard method after coronary catheterization of pigs) with subsequent thrombosis distal and proximal to access site and to ensure the patency of the femoral artery, we set the closure device, as a compromised solution, and performed the control angiography from carotid access. Nevertheless, the local places of the anchor and collagen were not entered into the histological analyses.

Severe spasm of the artery at the access site occurs usually at the time of puncture or multiple failed punctures, or due to catheter manipulation in a tortuous radial and subclavian artery. However, we intended to call attention to the local complications of the access site during and after catheterization, if puncture and catheterization were seemingly successful.

Conclusions

NO-eluting introducer sheaths prevent the acute, mechanically induced vasoconstriction of the access artery during cardiac catheterization and result in less thrombosis and local inflammation, contributing to vessel patency.

Table 4. Histomorphometric Results of the Femoral Arteries 1 Week After Coronary Intervention After NO-Eluting (NO-Sheath) and Control Sheath Placement (Control Sheath and Control + C-Sheath With Vasodilation Cocktail)

Sheath Groups (at 1-Week Follow-Up)	Lumen Area (mm^2)	Intimal Area (mm^2)	IEL Area (mm^2)	Media Area (mm^2)	EEL Area (mm^2)	Adventitia Area (mm^2)	%AS (%)
NO-sheath (n = 10 arteries)	3.32 ± 1.32	0.31 ± 0.31	3.63 ± 1.48	1.98 ± 0.96	5.61 ± 1.94	7.31 ± 2.61	7.9 ± 5.6
Control sheath (n = 10 arteries)	2.92* ± 1.39	0.47* ± 1.00	3.39 ± 1.61	2.01 ± 0.89	5.41 ± 1.53	7.16 ± 1.99	13.2* ± 15.7
Control + C-sheath (n = 8 arteries)	2.73* ± 0.77	0.86* ± 0.82	3.57 ± 0.94	2.23 ± 0.74	5.79 ± 1.25	7.44 ± 1.86	24.1* ± 13.7
p value	<0.05	<0.05	NS	NS	NS	NS	<0.01

The p values represent the results of analysis of variance. *p < 0.005 between NO-sheath versus control sheath and control + C-sheath by *t* test.
Abbreviations as in Tables 1 and 3.

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Key Words: drug-coating ■ introducer sheath ■ nitric oxide ■ percutaneous coronary intervention ■ radial artery.